The Yield of Mediastinoscopy with Respect to Lymph Node Size, Cell Type, and the Location of the Primary Tumor

Juan J. Fibla, MD, PhD, Laureano Molins, MD, PhD,* Carlos Simon, MD, PhD,† Javier Perez, MD,* and Gonzalo Vidal, MD**

Background: The aim of this study was to investigate the yield of cervical mediastinoscopy (CM) for pathologically diagnosed non-small cell lung cancer (NSCLC), with respect to lymph node size on computed tomography (CT), cell type, and the location of the primary tumor.

Methods: We reviewed 142 patients who underwent standard cervical mediastinoscopy from April of 1994 to June of 2003 for pathologically diagnosed NSCLC. The staging yield was determined by the percentage of "positive" CM (metastatic paratracheal or subcarinal nodes). Mediastinoscopy was performed when the lymph node diameter was >1 cm and, since 2001, whenever paratracheal or subcarinal lymph nodes were clearly seen on CT, regardless of size. Group A includes patients with lymph nodes on CT of ≥1 cm. Group B includes patients with lymph nodes of <1 cm. The χ^2 test was used for statistical analysis.

Results: We performed CM on 142 patients. There were 127 men (89.4%) and 15 women (10.6%). The mean age of the patients was 64.7 years (range, 38–83). The global yield was 28.2% (CM positive in 40 of 142 cases). The specific yield by groups was as follows, with respect to lymph node size: group A (lymph nodes >1 cm), 37.9%, and group B (lymph nodes <1 cm), 8.5% ($p < 0.01$). With respect to cell type, 16.3% were squamous tumors, 42.9% were adenocarcinomas ($p < 0.01$), 45.5% were large-cell carcinomas, and 44.4% were other types. With respect to the location of the primary tumor and T stage, there were no statistically significant differences ($p = 0.09$). When only patients with squamous tumors with no enlarged lymph nodes were considered, staging yield was 3.3% (one of 30), and 19.6% (20 of 102) of patients with a negative CM had positive mediastinal lymph nodes at the time of the resection. The yield was 9.8% (10 of 102 patients) in the territory accessible by CM at the time of the resection (true false negative), and 9.8% (10 of 102 patients) in the territory not accessible by CM.

Conclusion: Lymph node size and cell type of primary tumors should be taken into account when selecting patients for staging with standard MC in NSCLC. In patients with squamous-type tumors with lymph nodes <1 cm on CT, CM could be avoided because its low yield.

Key Words: Lung cancer, Staging, Mediastinoscopy.

(*J Thorac Oncol.* 2006;1: 430–433)

At present, surgery is the treatment option that offers the best survival results for patients with non-small cell lung cancer (NSCLC). For that reason, it is mandatory to perform accurate staging of these patients to treat them appropriately.[1] The staging of mediastinal lymph nodes is continuously evolving as new diagnostic tools appear.[2,3] The incidence of pathologic mediastinal nodal metastases (pN2) varies from 24.9% to 62%, depending on the series.[4,5] Computed tomography (CT) is the most commonly used noninvasive method for evaluating the mediastinum. However, among the numerous studies on the use of CT as a diagnostic or staging tool, the values of sensitivity and specificity have been relatively low.[6] In addition, mediastinal nodes with metastasis do not always appear enlarged on a CT scan. It is believed that about 17% of the patients with resectable NSCLC and no enlarged mediastinal lymph nodes are really pN2 at the time of surgery.[7] In a prospective study performed by Arita et al.,[8] this value rose to 21%. Positron emission tomography (PET) and endoscopic ultrasound transesophageal needle aspiration have achieved higher levels of accuracy than CT scans; however, its use is limited due to high cost and low availability.[9] Cervical mediastinoscopy (CM) is considered an invasive but safe method for the evaluation of mediastinal lymph nodes. Nevertheless, there is wide variability in the criteria for performing CM. Most surgeons perform a CM when enlarged mediastinal lymph nodes are present on the CT scan (minor diameter >1 cm). However, other surgeons routinely perform CM as a part of NSCLC staging, independently of radiographic abnormalities.[10]

We present the results of a review of our experience with the use of CM between 1994 and 2003, focusing on the yield of the procedure by groups.

PATIENTS AND METHODS

From April of 1994 to June of 2003, CM was performed in 142 patients with NSCLC. During that period, a total of 477 patients had surgery for lung cancer. Preoperative CT scans were performed on all patients. Mediastinal lymph

*General Thoracic Surgery Department, Sagrat Cor University Hospital, Barcelona, Spain; †General Thoracic Surgery Department, Gregorio Marañon Hospital, Madrid, Spain This manuscript was presented at the 11th World Conference on Lung Cancer, July 3–6, Barcelona, Spain.

Address for correspondence: Juan J. Fibla, M.D., Ph.D., General Thoracic Surgery Department, Sagrat Cor University Hospital, Viladomat 288, 08029 Barcelona, Spain; E-mail: juanjofibla@hotmail.com

ISSN: 1556-0864/06/0105-0430

nodes were considered enlarged if their minor diameter was >1 cm on CT scan. The CM procedure was carried out according to a standard technique.[11] General anesthesia and tracheal intubation with an armed single-lumen tube was employed. Patients were positioned in the dorsal decubitus position with a roll under the shoulders to provide extension of the cervical area. A transverse cervicotomy was performed. After the paratracheal fascia opening and finger blunt dissection along the trachea, the video mediastinoscope was inserted. The metal blunt-tipped suction-coagulation device and endoscopic graspers were used simultaneously for dissection of mediastinal structures. Endoscopic dissectors were also used when indicated. Lymph nodes of levels 2, 4, and 7 were identified and accessible for dissection and biopsy. Lymph nodes could be entirely enucleated in several instances. Fine needle aspiration was performed before biopsy if doubts existed about the possible vascular nature of the structure and for cytologic study. Minor hemorrhage was controlled by coagulation or compression with gauze.

The histologic diagnosis of primary lung cancer (NSCLC) was obtained with flexible fiber-optic bronchoscopy or transthoracic needle aspiration under CT guidance. The location of the tumor (142 cases) was the right upper lobe (77 cases), the right middle lobe (one case), the right lower lobe (21 cases), the left upper lobe (27 cases), and the left lower lobe (16 cases). The T stage (102 cases) was as follows: 10 were pT1, 61 were pT2, 17 were pT3, and 14 were pT4. Our initial strategy was to perform CM on all the patients with apparently operable NSCLC and mediastinal lymph nodes >1 cm on CT scan (group A). Later (since 2001), we performed CM whenever mediastinal lymph nodes were present on CT scan, regardless of size (group B). The staging yield was determined by the percentage of "positive" CM (metastatic paratracheal or subcarinal nodes) in each group. We analyzed global yield, yield according to mediastinal lymph node size on CT scan, yield according to the histologic origin of the primary NSCLC, and yield according to the primary lung tumor location.

RESULTS

CM was performed in 142 patients. There were 127 men (89.4%) and 15 women (10.6%). Median age was 64.7 years (range, 38–83).

There was no operative mortality associated with CM. No significant mediastinoscopy-related complications occurred. The global yield was 28.2% (40 tumor-positive CM of 142 CM procedures). Specific yield by different groups is shown in Table 1. There were statistical differences ($p < 0.01$) between lymph node size (groups A and B), and cell type groups (squamous tumor and adenocarcinoma).

There were no statistical differences between location of the tumor and T stage. When only patients with squamous tumors with no enlarged lymph nodes were considered, staging yield was 3.3% (one of 30 cases) ($p < 0.01$).

Of 102 (19.6%) patients with negative CM, 20 had positive mediastinal lymph nodes at the time of resection. Ten of 102 (9.8 %) were not accessible by CM (six aorto-pulmonary window [level 5], two para-aortic [level 6], one posterior subcarinal [level 7], and one pulmonary ligament [level 9]). Ten of 102 (9.8 %) were in the region of CM (three right lower paratracheal [level 4R], six anterior subcarinal [level 7], and one pretracheal [level 3]), considered as true false negative.

DISCUSSION

The future of patients with lung cancer is uncertain, with global estimated 5-year survival rates of approximately 14%.[12] In absolute terms, surgery is the only established method of cure for lung cancer. It is only possible, however, in a relatively small proportion of patients with the disease, mainly NSCLC stages I and II, with 5-year survival rates between 50% and 70%.[13] Mediastinal lymph node involvement, N2 disease, is a factor associated with a negative prognosis that directly influences the treatment strategy. The 5-year survival rate of patients with NSCLC and pN2 disease who had complete surgical resection of their tumors varies

TABLE 1. Yield of Cervical Mediastinoscopy According to Mediastinal Lymph Node Size, Cell Type, T Stage, and Laterality

	Group	Positive Mediastinoscopy/ No. of Patients	Yield (%)	p
	All the groups	40/142	28.2	
Lymph node size	Group B (<1 cm)	4/47	8.5	<0.01
	Group A (>1 cm)	36/95	37.9	
Cell type	Squamous	13/80	16.3	<0.01
	Adenocarcinoma	18/42	42.9	
	Large-cell carcinoma	5/11	45.5	
	Others	4/9	44.4	
T stage	T1	3/12	25	NS (0.5)
	T2	20/91	22	
	T3	4/18	22.2	
	T4	6/14	42.9	
Tumor location	Right	32/99	32.3	NS (0.09)
	Left	8/43	18.6	
	Squamous + clinical N0	1/30	3.3	

NS, not significant.

between 19% and 35%, depending on the series.[14] The CT scan is the most widely available and commonly used method of evaluating the mediastinum in NSCLC staging. Based on a meta-analysis of 42 studies conducted in 1990, the most widely accepted criterion for malignant involvement of lymph nodes is a short axis diameter of >1 cm on a transverse CT scan.[15] A recent systematic review by Toloza et al.[16] evaluated 20 studies that used standard CT scanning for staging the mediastinum. The pooled sensitivity was 57% and the pooled specificity was 82%. Marked heterogeneity in the sensitivity and specificity of the individual studies was noted. Subsequent investigations have produced similar findings. Most surgeons are aware of the importance of tissue confirmation when there is mediastinal involvement. In fact, evidence confirms that despite technical advances, no single imaging method alone is conclusive in evaluating potential mediastinal involvement in apparently operable lung cancer and routine clinical conditions.[17] Surgical staging of the mediastinum by CM has been historically the standard procedure for evaluating mediastinal lymph nodes. Its high specificity is difficult to be match with imaging methods. Inaccurate staging results in an understaged patient and in the loss of the opportunity for preoperative chemotherapy.[18] When the patients are up-staged, they may be submitted to an unnecessary preoperative chemotherapy and lose the opportunity for curative surgical resection.[19]

However, CM has limitations; it cannot stage the whole mediastinum, and its sensitivity in the detection of metastases in the accessible nodes varies between 79% and 93%.[20] In our series, the sensitivity was 90.2%.

Some authors have reported the results of CM performed in the early stage of NSCLC. Global yield of CM has varied from 36% to 7% in various series.[21–26] In our review, global yield was 28.2% ($n = 142$). This heterogeneity can be related to several factors affecting yield that, if identifiable, could be a guide for establishing widely accepted criteria for CM indications.[27]

Primary Tumor Histology

One of the factors that apparently most affects the yield of CM is NSCLC cell type. In our review, we observed a global yield of 28.2%. In the adenocarcinoma group, CM was tumor positive in 42.9% of the cases versus 16.3% in squamous carcinoma ($p < 0.01$). In the large-cell carcinoma group, 45.5% were tumor positive and 44.4% positive for other cell types.

Several authors have demonstrated a high rate of pN2 disease in adenocarcinomas. In a study by Choi et al.,[26] the yield of CM was 11.5% in the adenocarcinoma group and 3.3% in the squamous carcinoma group. De Leyn et al.[23] demonstrated that the prevalence of positive CM was statistically higher in adenocarcinoma than in squamous carcinoma. We have only identified one study that found no differences between the histologic subtypes. Funatsu et al.[25] showed a yield of 9% for CM for adenocarcinomas and 7% for squamous carcinomas. Based on these results, some authors, such as Nakanishi and Yasumoto,[28] are in favor of the routine surgical mediastinal staging in the cases of adenocarcinoma because in their series this histologic type represented 54% of the unsuspected pathologic N2 (pN2) that was diagnosed at thoracotomy. Suzuki et al.[29] in their group of adenocarcinomas, found 17.9% of pN2p-pN3 not seen on CT scan, concluding that routine CM was a correct staging strategy in this type of tumor.

According to our experience and based on most of the published studies, we believe that adenocarcinoma has a higher tendency to involve mediastinal lymphatic nodes. For the large-cell carcinoma group, the yield of CM was also high (45.5%); however, the number of patients was too low to draw firm conclusions (five of 11).

Mediastinal Lymph Node Size

Many thoracic surgeons hesitate to perform mediastinoscopy in patients who have no enlarged mediastinal nodes on preoperative CT scans.[10] On the other hand, there are studies advocating routine preoperative CM in all patients with apparently operable NSCLC, even without enlarged mediastinal lymph nodes.[26] The main justification for this policy is that 17% of the cases in which there are no enlarged mediastinal nodes on CT scan have pN2 disease at thoracotomy.[30] The Canadian Lung Oncology Group in 1995 conducted a randomized, controlled trial involving 685 patients with apparently operable NSCLC who underwent either CM or CT. Their results showed no advantage in the practice of routine CM in clinical N0 patients.[31] Based on current evidence, patients with apparently operable lung cancer should all have a CT scan of the chest, and those with nodes >1 cm should undergo CM, whereas the remainder can proceed directly to thoracotomy. There is limited evidence that a combined approach, CT plus CM, in all patients might further decrease the number or unnecessary thoracotomies. In the present study, the yield of CM in group B (lymph nodes <1 cm) was 8.5% ($n = 47$), whereas in group A (lymph nodes >1 cm), the yield was 37.9% ($n = 95$) ($p < 0.01$). According to our data, we consider that the size of mediastinal lymph nodes influences the yield of CM, and the combination of squamous carcinoma and lymph nodes <1 cm obviates performing CM given its low yield (3.3%) ($p < 0.01$).

Primary Tumor Location and T Stage

Coughlin et al.[22] analyzed their results according to the location of the primary lung tumors. They reported that 32.65% of right-sided lung tumors had positive mediastinal lymph nodes at CM, whereas left-sided lung tumors had a positivity rate of 13.73%. In our study, we obtained similar results, with a tumor-positive rate of 32.3% for right-sided lung tumors and 18.6% for left-sided lung tumors, but the differences were not statistically significant.

Rocha et al.[32] documented that the location of lung cancer (i.e., in the lower lobe) was significant in the incidence of pN2 and played a role with regard to up-staging. The incidence of nodal involvement seem to correlate with T stage. In our series, there were no differences between tumor location and T stage (Table 1).

CONCLUSION

The size of mediastinal lymph nodes and the histology of the primary tumor must be taken into account when

selecting patients for staging CM in NSCLC. The probability of a CM lymph node–positive biopsy increases when the primary tumor is an adenocarcinoma or a large-cell carcinoma and in lymph nodes >1 cm. We do not recommend this approach on patients with squamous-type tumors without nodal enlargement on CT because of its low yield.

REFERENCES

1. Rusch VW. Evidence-based outcomes for patients with non-small cell lung cancer undergoing resection. *Semin Respir Crit Care Med* 2000; 21:433–442.
2. Eloubeidi MA, Cerfolio RJ, Chen VK, et al. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg* 2006;79:263–268.
3. DeCamp JrMM Ashiku S, Thurer R. The role of surgery in N2 non-small cell lung cancer. *Clin Cancer Res* 2006;11:s5033–s5037.
4. De Leyn P, Decker G. Surgical treatment of non-small cell lung cancer. *Rev Mal Respir* 2004;21:971–982.
5. Niizeki H, Morikawa T, Okushiba S, et al. Survival and prognostic factors in resected cN2-pN0 non-small cell lung cancer. *Ann Thorac Cardiovasc Surg* 2004;10:9–13.
6. Wallace MB, Ravenel J, Block MI, et al. Endoscopic ultrasound in lung cancer patients with a normal mediastinum on computed tomography. *Ann Thorac Surg* 2004;77:1763–1768.
7. Luke WP, Pearson FG, Todd TR, et al. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. *J Thorac Cardiovasc Surg* 1986;91:53–56.
8. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. *Thorax* 1995;50: 1267–1269.
9. Takamochi K, Yoshida J, Murakami K, et al. Pitfalls in lymph node staging with positron emission tomography in non-small cell lung cancer patients. *Lung Cancer* 2006;47:235–242.
10. Smulders SA, Smeenk FW, Janssen-Heijnen ML, et al. Surgical mediastinal staging in daily practice. *Lung Cancer* 2006;47:243–51.
11. Molins L.. Mediastinoscopy. *Med Clin (Barc)* 1989;93:498–500.
12. Humphrey EW, Smart CR, Winchester DP, et al. National survey of the pattern of care for carcinoma of the lung. *J Thorac Cardiovasc Surg* 1990;100:837–843.
13. Birim O, Kappetein AP, Goorden T, et al. Proper treatment selection may improve survival in patients with clinical early-stage nonsmall cell lung cancer. *Ann Thorac Surg* 2006;80:1021–1026.
14. Friedel G, Steger V, Kyriss T, et al. Prognosis in N2 NSCLC. *Lung Cancer* 2004;45(suppl 2):s45–s53.
15. Dales RE, Stark RM, Raman S. Computed tomography to stage lung cancer: approaching a controversy using metaanalysis. *Am Rev Respir Dis* 1990;141:1096–1101.
16. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003;123(1 suppl):137S–146S.
17. D'Cunha J, Herndon JE, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage I non-small cell lung cancer: results from CALGB 9761, a prospective trial. *Lung Cancer* 2006;48: 241–246.
18. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994;330:153–158.
19. Van Schil P, Van Meerbeeck J, Kramer G, et al. Morbidity and mortality in the surgery arm of EORTC 08941 trial. *Eur Respir J* 2006;26:192–197.
20. Kernstine KH, Mclaughlin KA, Menda Y, et al. Can FDG-PET reduce the need for mediastinoscopy in potentially resectable non-small cell lung cancer? *Ann Thorac Surg* 2002;73:394–401.
21. Martin de Nicolas J, Gomez-Caro A, Moradiellos FJ, et al. Importance of routine mediastinal staging in women with non-small cell lung cancer. *Arch Bronconeumol* 2006;41:125–129.
22. Coughlin M, Deslauriers J, Beaulieu M, et al. Role of mediastinoscopy in pretreatment staging of patients with primary lung cancer. *Ann Thorac Surg* 1985;40:556–560.
23. De Leyn P, Vansteenkiste J, Cuypers P, et al. Role of cervical mediastinoscopy in staging of non-small cell lung cancer without enlarged mediastinal lymph nodes on CT scan. *Eur J Cardiothorac Surg* 1997; 12:706–712.
24. Jolly PC, Hutchinson CH, Detterbeck F, et al. Routine computed tomographic scans, selective mediastinoscopy, and other factors in evaluation of lung cancer. *J Thorac Cardiovasc Surg* 1991;102:266–270.
25. Funatsu T, Matsubara Y, Ikeda S, et al. Preoperative mediastinoscopic assessment of N factors and the need for mediastinal lymph node dissection in T1 lung cancer. *J Thorac Cardiovasc Surg* 1994;108:321–328.
26. Choi YS, Shim YM, Kim J, et al. Mediastinoscopy in patients with clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2003;75: 364–366.
27. Casali C, Stefani A, Natali P, et al. Prognostic factors in surgically resected N2 non-small cell lung cancer: the importance of patterns of mediastinal lymph nodes metastases. *Eur J Cardiothorac Surg* 2006;28: 33–38.
28. Nakanishi R, Yasumoto K. Combined thoracoscopy and mediastinoscopy for mediastinal lymph node staging of lung cancer. *Int Surg* 1996;81:359–361.
29. Suzuki K, Nagai K, Yoshida J, et al. Clinical predictors of N2 disease in the setting of a negative computed tomographic scan in patients with lung cancer. *J Thorac Cardiovasc Surg* 1999;117:593–598.
30. Rodríguez P, Santana N, Gámez P, et al. Mediastinoscopy in the diagnosis of mediastinal disease. An analysis of 181 explorations. *Arch Bronconeumol* 2003;39:29–34.
31. Canadian Lung Oncology Group. Investigation for mediastinal disease in patients with apparently operable lung cancer. *Ann Thorac Surg* 1995;60:1382–1389.
32. Rocha AT, McCormack M, Montana G, Schreiber G. Association between lower lobe location and upstaging for early-stage non-small cell lung cancer. *Chest* 2004;125:1424–1430.

